Remarks:

Reconsideration of the application is requested.

Claims 20 to 22, 25, 27, 28, 30, and 37 to 45 are now in the application. Claims 1 to 19 were cancelled in previous amendments. Claim 20 has been amended. Claims 37 to 45 have been added.

On pages 2 to 4 of the above-identified Office action, claim 20 has been rejected as being fully anticipated by U.S. 4,908,350 to Kramer et al. (hereinafter "Kramer '350") under 35 U.S.C. § 102.

As will be explained below, it is believed that the claims were patentable over the cited art in their original form and, therefore, the claims have not been amended to overcome the references.

Before discussing the prior art in detail, it is believed that a brief review of the invention as claimed, would be helpful. Claim 20 calls for, *inter alia*, a pharmaceutical composition consisting essentially of:

> a first substance comprising sodium chloride in an amount between about 1.5% and 6.9% (w/v);
>
> a second substance comprising at least one of hydroxyethyl starch, dextran, carboxymethyl starch, polyvinyl pyrrolidone (PVP), gelatin derivatives,

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condensed glucose, glucose, fructose, lactose, glycerin, xylitol, sodium alginate, N-2-hydroxypropylacrylamide, ethylene epoxide, polypropylene glycol, pectin, and pentahydroxyethyl starch, wherein said second substance is present in an amount between about 3 and 18 % total (w/v);

a third substance comprising at least one of sodium bicarbonate, potassium chloride, magnesium sulfate, calcium chloride, calcium gluconate, calcium lactate, sodium lactate, and Tris (Hydroxy methyl) aminomethane, **wherein said third substance is present in an amount between about 0 and 5.4 % total (w/v)**; and

an injection comprising at least one of water, physiological saline, balanced buffers, glucose solution, sodium lactate solution, Tris solution, and glucose and sodium chloride solution, wherein said injection is present in an amount between about 75.1 % and 95.5% total (w/v),

wherein the total sodium ion concentration does not exceed an equivalent sodium ion concentration of 6.9 % (w/v) sodium chloride solution.

The Examiner indicates on page 3 of the rejection that:

> The concentration of the crystalloid [in Kramer '350] is between about 1800 to 3000 mOsm (column 3, lines 43-45; see claim 1). It is noted that 1800 mOsm NaCl is about 5.3 w/v%, and 2400 mOsm NaCl is about 7 w/v% NaCl.
> . . .
> Further, **different hyperosmotic NaCl solutions were also used with 6% dextran 70, including 1200 mOsm** and 1800 mOsm NaCl (see column 6, lines 36-41). It is noted that 1200 mOsm converts to about 3.5 wt/v% NaCl, and 1800 mOsm converts to about 5.3 w/v% NaCl. (Emphasis added by applicant.)

It is true that Kramer '350 "used" different hyperosmotic NaCl solutions and discloses such use in Table II. Based upon such alleged "use," the Examiner believes that Kramer '350 anticipates the less than 5 w/v% NaCl disclosed in claim 20. However, just because Kramer '350 "used" such lower mOsms

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solutions in a study, does not mean that Kramer '350 adopted, recommended, or espoused using values less than 1800 mOsms. In fact, Kramer '350 specifically not only fails to recommend use of a solution of less than 1800 mOsms, Kramer '350 specifically and only counsels using hyperosmotic concentrations of **greater than 1800 mOsms**!

Applicant has reviewed the entire disclosure of Kramer '350. Kramer '350 mentions mOsms in claims 1, 3, 4, 7, 8, 10, and 11 and on col. 2, lines 64 to 65, col. 2, lines 13 to 17 and 54 to 55, col. 3, lines 43 to 45, col. 4, lines62, 63, and 66, col. 6, lines 37 to 65, col. 7, line8, 33 to 23, 29, and 60 to 62. **Nowhere does Kramer '350 suggest use of solutions having less than 1800 mOsms**. *Each and every instance* in Kramer '350 indicates to one having ordinary skill in the art that Kramer '350 teaches towards hyperosmotic concentrations in excess of 1800 mOsms and that "[c]ardiovascular response generally *improved* as osmolarity *increased* to 2400 mOsms." Col. 6, lines 43 to 44 (emphasis added by applicant). Thus, Kramer '350 teaches increasing osmolarity *above* 1800 mOsms. In contrast thereto, the invention of the instant application teaches *decreasing osmolarity below 1800 mOsms*.

Experiments have been conducted to prove that a hyperosmotic concentration in excess of 1800 mOsms does not have as good efficacy as a hyperosmotic concentration less than 1800 mOsms.

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Attached hereto is a Declaration of the inventor Zhao Chao-Ying, who conducted the experiments substantiating this conclusion. These conclusions are supported by findings that are attached to Dr. Zhao's Declaration as Exhibit A.

The trial data contained in the Tables 1 to 6 of Exhibit A, in combination with the results disclosed by Kramer '350, prove that Kramer '350's teaching toward a higher concentration of NaCl is not as good as the opposite teaching of the invention of the instant application -- to wit, towards a lower concentration.

Table II of Kramer '350 shows that different concentration of NaCl solution (from 300 to 3600mOsms) leads to different results. The figures therein for Cardiac Output (CO) is *over* the desired baseline only for groups having been administered at least 1800 mOsms when the hypertonic solution has been infused at 10 min, **and for the group of 3600 mOsms when the hypertonic solution has been infused at 60 min**. The values of CO in other groups are all *below* the desired baseline. This is especially true for Kramer '350's 300 and 1200 mOsms results. Kramer '350 explains that for the group administered with 3600 mOsms, convulsion occurred. Based upon the serious detrimental effects occurring at 3600 mOsms, Kramer '350 teaches a preferred NaCl concentration of between 1800 to 2400 mOsms.

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The experimental results, as shown in Table 3 of Exhibit A, indicate that the affect of 7.5% NaCl (2400mOsms) in Group 1 (G1) is not as good as the affect of 5.3% NaCl (<1800mOsms) in Groups 2 or 3 (G2, G3) or that of 3% NaCl in Groups 4 or 5 (G4, G5) because the values of CO in the latter two (G2 to G5) are desirably larger than the group of 7.5% NaCl (G1).

The results have been so conclusive that medical authorities in China have approved the inventor's composition for treating shock with a NaCl concentration under 1800 mOsms. It is significant to note that the inventor's composition has no cases of side effects, which is not true for the Kramer '350 composition.

On pages 4 to 9 of the above-identified Office action, claims 20, 22, 25, and 27 have been rejected as being obvious over U.S. 5,443,848 to Kramer et al. (hereinafter "Kramer '848") in view of Kramer '350 under 35 U.S.C. § 103.

As will be explained below, it is believed that the claims were patentable over the cited art in their original form and, therefore, the claims have not been amended to overcome the references.

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Kramer '350 does not disclose or suggest the invention of the instant application as set forth in claim 20. Claims 22, 25, and 27 are dependent upon claim 20. Thus, these claims are allowable over Kramer '350 for the reasons stated above, which arguments are hereby incorporated by reference.

Kramer '848 has been cited for that proposition that the composition contains a mixture of sodium chloride (NaCl) and sodium acetate (NaAc) in different proportions, wherein the total osmolarity of the concentration of the two components is in excess of 500 mOsms, such as 1000 mOsms or 2400 mOsms. It is noted that the phrase "sodium acetate" has been removed from the claims. Therefore, this rejection is moot. But, additionally, Kramer '848 does not overcome the deficiencies of Kramer '350 when a comparison is made between Kramer '350 and the invention of the instant application. Thus, the combination of Kramer '350 and Kramer '848 does not suggest the invention of the instant application as set forth in claims 20, 22, 25, and 27.

A critical step in analyzing the patentability of claims pursuant to 35 U.S.C. § 103 is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614,1617 (Fed. Cir. 1999).

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Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." Id. (quoting W.L. Gore & Assocs. Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983)).

Most if not all inventions arise from a combination of old elements. See In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453,1457 (Fed. Cir. 1998). Thus, every element of a claimed invention may often be found in the prior art. See id. However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. See id. Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the Examiner. See In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 163.5, 1637 (Fed. Cir. 1998); In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125,1127 (Fed. Cir. 1984).

The motivation, suggestion, or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the

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problem to be solved. See Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617. In addition, the teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. See WMS Gaming, Inc. v. International Game Tech., 184 F.3d 1339, 1355, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981) (and cases cited therein). Whether an examiner relies on an express or an implicit showing, the Examiner must provide particular findings related thereto. See Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617. Broad conclusory statements standing alone are not "evidence." Id. When an examiner relies on general knowledge to negate patentability, that knowledge must be articulated and placed on the record. See In re Lee, 277 F-3d 1338, 1342-45, 61 USPQ2d 1430, 1433-35 (Fed. Cir. 2002).

Upon evaluation of the Office action, it is respectfully believed that the evidence adduced is insufficient to establish a *prima facie* case of obviousness with respect to the claims.

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Applicants respectfully believe that any teaching, suggestion, or incentive possibly derived from the prior art is only present with hindsight judgment in view of the instant application. "It is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps. . . . The references **themselves** must provide some teaching whereby the applicant's combination would have been obvious." In re Gorman, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991) (emphasis added). Here, no such teaching is present in either Kramer '350 or Kramer '848.

On pages 9 to 10 of the above-identified Office action, claim 20 has been rejected as being obvious over WO 90/08500 (hereinafter "WO'500") under 35 U.S.C. § 103.

As will be explained below, it is believed that claim 20 was patentable over the cited art in its original form and, therefore, the claim has not been amended to overcome the reference.

The hypertonic arginine composition of WO'500 requires L-arginine to be present. WO'500 clearly provides that in fact, conventional wisdom in view of the state of knowledge concerning the effects of L-arginine would have predicted lower blood pressure by producing more vasodilation through

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greater NO release[, u]se of L-arginine therefore would seem to be contra-indicated in treatment of hypotensive shock." Every example and claim of WO'500 **requires** the presence of L-arginine.

WO'500 discloses a hypertonic composition containing L-arginine in addition to sodium chloride as low as 6% (w/v) [see page 5, lines 14 to 15, and claim 14], hetastarch (hydroxyl ethyl starch), and, of course, the injection liquid [see page 4, line 22].

In the compositions disclosed by WO'500, the L-arginine is present in the range of 0.3 to 7.5 g/100ml. The compositions of WO'500 are said to be superior to hypertonic saline solutions (7.2 to 7.5% NaCl w/v) and a 7.5% hypertonic saline 6% dextran solution [page 7, lines II-page 8, line 2] for the treatment of traumatic brain injury (TBI) and hypotension (shock) *because of* the presence of L-arginine. The L-arginine solutions of WO'500 are designed for the treatment of a patient having the combined injury of TBI and hemorrhage. TBI releases neuroexcitatory amines that increase the oxygen needs of the brain, while tissue swelling and intracranial hemorrhage increases the intracranial pressure (ICP) that reduces cerebral blood flow (CBF). WO'500 further notes that hypotension or reduced mean arterial pressure (MAP) further reduces brain CBF. See WO at 1/29 to 2/5. Accordingly, WO'500

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sought a composition that, for a patient with combined TBI and hemorrhage, would, ideally, *lower* the ICP, *selectively vasodilate the brain* (but not other vessels of the body), and correct and prevent hypotension and hemorrhagic shock.

WO'500 achieved its invention by adding to a NaCl hypertonic solution (NaCl 6-8g/100ml) L-arginine in a range of 0.3-7.5g/100mo [See page 4, lines 9 to 11 and page 5, lines 12 to 15]. WO'500 did this to achieve reduction of ICP and vasodilate the brain even though, L-arginine being a NO generation source, the addition of L-arginine would be expected to reduce to hypertonic saline solution's effectiveness for the correction and prevention of hypotension and hemorrhagic shock.

Hence, as can be seen from the description of WO'500, because L-arginine is converted by NO synthase, an enzyme in brain and blood vessels, into NO, which is a potent vasodilator (page 11, lines 21 to 24), L-arginine would be expected to lower the ability of a hypertonic saline solution to elevated the blood pressure in a patient experiencing hypotensive shock (page 3, line 30-page 4, line 2). Accordingly, this blood pressure lowering effect of L-arginine would seem to dictate a need to increase the NaCI content of the hypertonic saline solution to which it is added.

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Because WO'500 relies exclusively on the benefits of L-arginine, it is self-evident that L-arginine materially affects the basic characteristics of a hypertonic saline solution, *i.e.*, namely, the blood pressure elevating property of the hypertonic saline solution.

The invention of the instant application is an improved hypertonic saline (NaCl) solution, with the improvement being a limiting of the maximum of free sodium ion in the solution to not greater than that of a 6.9% (w/v) NaCl solution. In the invention of the instant application, the content of free sodium ion in a hypertonic saline solution is reduced so as to lessen toxicity to the organism, and to reduce the rupture of blood cells and other side effects, while maintaining and/or enhancing its ability to increase the blood pressure of a person in shock by employing hydroxyethyl starch in conjunction with NaCl and generally in greater amounts than NaCl.

As set forth in the Declaration of Dr. Zhao, WO'500 was willing to suffer the negative effects of L-arginine upon the blood pressure elevating properties of a hypertonic saline-hydroxyethyl starch solution for the collection of hypotension and hemorrhagic shock to secure the beneficial effects that L-arginines exerts upon the cerebral blood flow (CBF) and infracranial pressure (ICP) in the case of TBI. Dr. Zhao

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concludes that inclusion of L-arginine materially affects the novel and basic characteristics of a hypertonic saline-hydroxyethyl starch composition that is the subject of claim 20.

The Examiner, without any evidentiary support, supposes that L-arginine would not materially affect the novel and basic characteristics of applicant's invention. Dr. Zhao has contradicted that unsupported assertion, which must be accepted.

Inclusion of L-arginine in the claimed compositions would materially affect their characteristics - *i.e.*, it would reduce the blood pressure restoring ability of the compositions because L-arginine is a producer of the potent vasodilator NO. Accordingly, as was the question in the case of Ex parte Davis, 80 USPQ 448, 450 (Bd Pat App & Int 1949), namely:

> In the present case where the claims recite three ingredients and the reference discloses four, the important question is whether the term "consisting essentially of" excludes that fourth ingredient.

So too it is the question here. And, as in Davis, the answer should be the same -- "that it does."

Claim 22 provides that the second substance of claim 21

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"comprises hydroxyethyl starch, at least 10% of which has a molecular weight of about 25,000-45,000 atomic mass units." There is no disclosure or suggestion in WO'500 that when a HES is utilized in a hypertonic NaCl solution that at least 10% of such HES should have a molecular weight of 25,000-45,000 atomic mass units. The Examiner has cited no evidence to establish that "well known, physiologically acceptable hydroxyethyl starch" has at least 10 % of its content in a molecular weight range of 25,000 - 45,000 atomic mass units. Claim 22 requires at least 10 % of the HES to have a molecular weight of 25,000 - 45,000 atomic mass units. There being no evidence that this characteristic is obvious for a HES used in a hypertonic NaCl solution, claim 22 can not be properly rejected without support.

Clearly, WO'500 does not show a composition as recited in claim 20 of the instant application.

Claim 45 has been added. It is the same as claim 20 except "consisting essentially of" has been replaced with "consisting of." Because claim 45 excludes L-arginine, WO'500 cannot disclose or suggest the invention of this claim and claim 46 is allowable.

It is accordingly believed to be clear that none of the references, whether taken alone or in any combination, either

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show or suggest the features of claim 20. Claim 20 is, therefore, believed to be patentable over the art. The dependent claims are believed to be patentable as well because they all are ultimately dependent on claim 20.

Finally, applicants appreciatively acknowledge the Examiner's statement that claims 21, 28, and 30 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. In light of the above, applicants respectfully believe that rewriting of the claims is unnecessary at this time.

Claim 42 has been added and is a combination of original claims 20 and 21.

Claim 43 has been added and is a combination of original claims 20 and 28.

Claim 44 has been added and is a combination of original claims 20 and 30.

Based upon the above, these new claims are believed to be allowable.

In view of the foregoing, reconsideration and allowance of claims 20 to 22, 25, 27, 28, 30, and 37 to 45 are solicited.

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In the event the Examiner should still find any of the claims to be unpatentable, counsel would appreciate receiving a telephone call so that, if possible, patentable language can be worked out.

If an extension of time for this paper is required, petition for extension is herewith made.

The extension fee for response within a period of two (2) months pursuant to Section 1.136(a) in the amount of $215.00 in accordance with Section 1.17 and the amount of $88.00 for two additional independent claims in excess of three are enclosed herewith.

Please charge any other fees that might be due with respect to Sections 1.16 and 1.17 to the Deposit Account of Lerner and Greenberg, P.A., No. 12-1099.

Respectfully submitted,

For Applicants

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